19 May 2003, Volume 22, Number 20, Pages 3099-3112

Table of contents Previous Article Next PDF

Review

Ultraviolet radiation and cutaneous malignant melanoma

Chamelli Jhappan[1], Frances P Noonan[2] and Glenn Merlino[1]

[1]*Molecular Genetics Section, Laboratory of Molecular Biology, National Cancer Institute, Bethesda, MD 20892-4264, USA*

[2]*Laboratory of Photobiology & Photoimmunology, Department of Environmental and Occupational Health, School of Public Health and Health Services, George Washington University Medical School, Washington, DC 20037, USA*

Correspondence to: G Merlino, E-mail: gmerlino@helix.nih.gov

Abstract

Recent years have seen a steady rise in the incidence of cutaneous malignant melanoma worldwide. Although it is now appreciated that the key to understanding the process by which melanocytes are transformed into malignant melanoma lies in the interplay between genetic factors and the ultraviolet (UV) spectrum of sunlight, the nature of this relation has remained obscure. Recently, prospects for elucidating the molecular mechanisms underlying such gene–environment interactions have brightened considerably through the development of UV-responsive experimental animal models of melanoma. Genetically engineered mice and human skin xenografts constitute novel platforms upon which to build studies designed to elucidate the pathogenesis of UV-induced melanomagenesis. The future refinement of

these *in vivo* models should provide a wealth of information on the cellular and genetic targets of UV, the pathways responsible for the repair of UV-induced DNA damage, and the molecular interactions between melanocytes and other skin cells in response to UV. It is anticipated that exploitation of these model systems will contribute significantly toward the development of effective approaches to the prevention and treatment of melanoma.

Oncogene (2003) **22,** 3099–3112.
doi:10.1038/sj.onc.1206450

Keywords

cell cycle arrest; DNA damage response; DNA repair; melanoma; transgenic mice; UV radiation

Clinical and epidemiological background

It has been almost 200 years since Parisian physician Rene Laennac's first report of melanoma in Europe. It was in the 1812 publication of his findings where the word 'melanoma' was first used by Laennac to describe a disease that recently would exhibit a dramatic rise in appearance, with a persistent worldwide annual increase in incidence of 3–7% per year in Caucasian populations with light-colored skin. In the United States alone studies show that the lifetime risk of developing malignant melanoma is 1 in 90 with a mortality rate of 1 in 400, and that the melanoma incidence rose 132% during the period 1979–1998 (Howe *et al.*, 2001; Jemal *et al.*, 2001). Statistics from a number of other countries have also demonstrated a rise in the incidence of melanoma (Armstrong and Kricker, 1994; Bennett and Hall, 1994; Parker *et al.*, 1997; Bardeesy *et al.*, 2000; Marks, 2000; Insinga *et al.*, 2001; Kaskel *et al.*, 2001).

Melanoma arises from the malignant transformation of the pigment producing melanocytes, which are located and evenly distributed in the basal epidermal layer of human skin. Melanocytes represent the second

largest cell population in the epidermis at 1–2%, greatly outnumbered by keratinocytes, which make up the largest group of cells at over 95% of the total epidermal cell population (Reedy *et al.*, 1998; Yaar and Gilchrest, 2001). Melanomas currently are classified histologically based upon their location and stage of progression. Malignant melanoma *in situ* and microinvasive malignant melanoma are confined to the epidermis, consisting of solitary and variably sized nests of atypical melanocytes, and demonstrating a radial growth pattern. The more aggressive and potentially lethal invasive malignant melanoma is characterized by a vertical growth phase, penetrating both the upper layer of the epidermis and the underlying dermal layer, representing a condition with high potential for metastatic spread. Metastatic melanoma can colonize both nonvisceral organs, such as the skin and lymph node, as well as visceral sites, such as lung, liver, bone, brain and small intestine (Elder, 1987; Barnhill and Mihm, 1993).

As in most types of cancers, there are two factors that present significant risk for melanoma in humans: genetic predisposition and exposure to environmental factors. Individuals from families with a demonstrated history of melanoma are at significant risk for developing this malignancy, representing from 5–12% of all reported cases (Haluska and Hodi, 1998; Goldstein and Tucker, 2001). As early as 1857, William Norris, a British general practitioner, published an article entitled 'Eight cases of Melanosis with Pathological and Therapeutical Remarks on that Disease' (Norris, 1857; Bennett and Hall, 1994). Here he presented several novel insights into the genesis and treatment of melanoma and made the profound observation that a family history was associated with the disease as presented by some of his patients, thus leading him to conclude that melanoma probably had a familial component. Interestingly, in the same publication, Norris noted that the majority of his patients had light-colored hair and pale complexions. Norris' observation in 1857 has stood the test of time and epidemiological

studies in the 20th century have shown that constitutional factors such as skin color and genetic predisposition influence melanoma formation. Indeed, fair-skinned people who freckle or sunburn easily without tanning and have blond or red hair present a higher risk of developing melanoma than individuals with darker skin (Evans *et al.*, 1988; Garbe *et al.*, 1994; Langley and Sober, 1997). It is now widely accepted that total risk of melanoma is determined through the interplay between such genetic factors and exposure to sunlight. For example, melanoma incidence in fair people is inversely related to latitude of residence with melanoma incidence peaking in Australia, a tropical and subtropical country with a majority of its population being fair skinned (Armstrong, 1988; de Gruijl, 1999; Marks, 2000). Moreover, it was recently reported that individuals living in Australia carrying inactivating mutations in CDKN2A, encoding the key melanoma suppressor gene p16INK4a, were at the highest risk for melanoma (Bishop *et al.*, 2002).

The Australian physician VJ McGovern was probably the first to suggest that sunlight could be an agent with a potential role in melanoma formation. In 1952, in an article entitled 'Melanoblastoma', McGovern (1952) noted that 'The person predisposed to malignant transformation of a mole is the fair person with pale skin who does not tan well on exposure to light, but who freckles readily'. Later epidemiological studies have confirmed McGovern's observation, and it is now believed that the majority of all melanoma cases are caused, at least in part, by excessive exposure to sunlight (Armstrong and Kricker, 1995; Armstrong *et al.*, 1997; MacKie, 1998; Marks, 2000; Rigel and Carucci, 2000; Jemal *et al.*, 2001). Notably, in contrast to squamous call carcinoma, it appears that melanoma risk is not associated with cumulative, but rather with more intense, intermittent exposure to sunlight. For example, the greatest increases in incidence of melanomas have been seen in the regions of the body subjected to intermittent exposure, such as the torso in men and the lower legs in women. Indeed, it is likely that abrupt changes

in sunlight exposure, such as experienced by people who travel recreationally to sunny locales in the middle of winter, is a causal factor in the increase in melanoma incidence observed in recent years. Epidemiological data have also suggested that a history of exposure to large doses of sunlight sufficient to cause sunburn in childhood is a particularly important melanoma risk factor (Holman *et al.*, 1983; Elwood and Jopson, 1997; Autier and Dore, 1998; Whiteman *et al.*, 2001). This review will focus primarily on sunlight and its ultraviolet (UV) radiation composition, how it damages skin, how the skin responds to that damage, and which current animal models best represent the sum total factors known to contribute to melanomagenesis in humans.

Sunlight and the damage it causes

Sunlight is a continuous spectrum of electromagnetic radiation that can be divided into three major regions of wavelength: the infrared, visible and UV. The region representing UV radiation, the most significant region of sunlight with respect to skin cancer, lies in the range of 200–400 nm, just above visible light at 400–700 nm. UV radiation can be further subdivided into UVA (320–400 nm), UVB (280–320 nm) and UVC (200–280 nm) wavebands. The UVC contribution to the development of skin cancers is considered negligible, since it is prevented from reaching the surface of the earth by the atmospheric ozone layer that blocks UV light below about 300 nm. Unlike UVC, UVA and UVB both reach the earth's surface in large enough amounts to cause harmful biological effects on the skin. UVB is considered to represent the most carcinogenic waveband, inducing erythema, or sunburn, historically associated with skin cancer risk. Nucleic acids and proteins both absorb light within the UVB range, peaking at 260 and 280 nm, respectively. Absorption of UVB by DNA causes damage that, if not repaired, can become initiating mutations in skin cancer (Figure 1). UVB causes two types of DNA lesions: the 6–4 photoproducts, generated between adjacent pyrimidine residues, and pyrimidine or

cyclobutane dimers, formed specifically between adjacent thymine (T) or cytosine (C) residues. The pyrimidine dimers are formed between the C-4 and C-5 carbon atoms of any two adjacent pyrimidines; the double bonds become saturated, giving rise to a four-membered ring (Tornaletti and Pfeifer, 1996; Matsumura and Ananthaswamy, 2002). The 6–4 photoproducts are formed between the 5' six position and the 3' four position of two adjacent pyrimidines, most often between TC and CC residues. Both lesions are most abundant where there are a string of pyrimidine residues. Pyrimidine dimers are considered to be more carcinogenic than the 6–4 photoproducts, forming almost three times as often and being repaired less efficiently (Rosenstein and Mitchell, 1987; You *et al.*, 2001). Both types of lesions can lead to genetic mutations such as the C→T or CC→TT transitions; the latter mutation represents the hallmark of UV-induced mutagenesis. In addition to these signature transitions, UVB can cause C→A and G→T transversions and DNA strand breaks, but the significance of this type of UV damage *in vivo* remains largely unresolved (Rosenstein and Mitchell, 1987; Linge, 1996; Cleaver and Crowley, 2002; Matsumura and Ananthaswamy, 2002).

Although UVA is the predominant component of sunlight to which humans are exposed, its role in skin cancer, including melanoma, is not nearly as well documented as UVB and is currently controversial. UVA exposure can also come from other sources such as sunlamps commonly used in tanning salons. Since UVA has longer wavelengths than UVB, it can penetrate deeper into the skin and, unlike UVB, pass through glass windows. A recent study demonstrated that summer clothing proved surprisingly ineffective as a barrier to UVA radiation, and that such clothing permitted a larger percent transmission of UVA than UVB (Kaidbey and Kligman, 1979; Bruls *et al.*, 1984; Wang *et al.*, 2001a). These two components of sunlight also have different biological effects. While UVB has been shown to be a thousand times more effective at causing sunburn than UVA radiation, UVA

proved to be much more effective at inducing immediate pigmentation darkening (IPD) and persistent pigment darkening (PPD) (Irwin *et al.*, 1993; Wang *et al.*, 2001b). Both IPD and PPD occur in dark-skinned individuals in response to UVA exposure, with IPD lasting a matter of minutes and PPD persisting for several hours postexposure. Since UVA is capable of penetrating deeper into skin exposed to sunlight, a higher percentage of UVA is capable of reaching melanocytes in human skin compared to UVB. Like UVB, UVA is able to mutate DNA. However, unlike UVB, UVA-mediated damage occurs indirectly through UV radiation absorption by non-DNA endogenous sensitizers, generating reactive oxygen species (ROS) (reviewed by Black *et al.*, 1997; Cadet *et al.*, 1997; Scharffetter-Kochanek *et al.*, 1997). The presence of such oxygen radicals can in turn lead to DNA damage, breaks and, ultimately, mutations. A particularly mutagenic species produced by UVA-induced oxidation of guanine is 8-hydroxyguanine (Amstad *et al.*, 1994; Runger *et al.*, 1995).

One of the most important questions yet to be resolved is whether the skin can be protected from the damaging effects of UV light by the presence of melanin. Melanoma occurs far less frequently in darker-pigmented individuals than in fair-skinned ones, with the differential being 10-fold in the United States. Furthermore, when dark-skinned individuals do develop melanoma, it is usually in a body part not frequently exposed to sunlight, such as the soles of the feet, palms of the hands, or nail beds. Melanin, a brown-black pigment, is synthesized in melanosomes within epidermal melanocytes, and then distributed to surrounding keratinocytes through melanocytic dendritic processes (reviewed by Hearing, 1999). Melanin can absorb UV photons and free radicals induced by UV before they interact with other cellular components (Kawada *et al.*, 1994; Khlgatian *et al.*, 2002; Ortonne, 2002). The highly organized presentation of melanosomes throughout the epidermis, characteristic of dark-colored skin, is reminiscent of a highly protective screen

designed to absorb and scatter damaging UV radiation.

There are two types of melanin: eumelanin, the main type present in dark skin and hair, and pheomelanin, the main type in red hair and freckled individuals. Eumelanin synthesis in melanocytes is stimulated by the binding of α-melanocyte-stimulating hormone (α-MSH) to the melanocortin-1 receptor (MC1-R), a G-protein-coupled cell surface receptor with seven transmembrane domains (Chhajlani and Wikberg, 1992; Mountjoy *et al.*, 1992; Hunt *et al.*, 1995). The type of melanin produced in melanocytes is influenced by the status of MC1-R; loss--of-function mutations in MC1-R prevent eumelanin production and are associated with most of the red-haired phenotypes observed in the human population (Box *et al.*, 1997; Smith *et al.*, 1998; Chakraborty *et al.*, 1999; Healy *et al.*, 2000; Schaffer and Bolognia, 2001; Taylor, 2002). In fact, the MC1-R helps regulate multiple melanocytic activites (see below), and nonfunctional MC1-Rs have been linked with enhanced sensitivity to the cytotoxic effects of UV as well as an increased incidence of melanoma (Valverde *et al.*, 1996; Palmer *et al.*, 2000; Kennedy *et al.*, 2001; Scott *et al.*, 2002).

Repair of UV-induced DNA damage

Cancer is one consequence of a cell's inability to repair DNA damage in an accurate and timely fashion. As previously described, UV radiation, especially UVB, is capable of introducing well-studied changes in DNA, which can be considered initiating events in oncogenesis. Initiation events may be inconsequential for a prolonged time period until other events, such as additional mutations or exposure to promoting agents, coax an aspiring cancer cell into a more progressive state, culminating in metastasis. Therefore, repairing the damage initially caused by sunlight becomes critical to preventing melanomagenesis and, indeed, skin cells are equipped with a variety of DNA repair pathways capable of removing DNA lesions depending on the type of UV-induced lesion. It

is worth noting that damage by UVA and UVB is repaired by different mechanisms (Cadet *et al.*, 1997; Hoeijmakers, 2001). While the oxidative lesions induced by UVA are repaired by base excision repair (BER), the bulky cyclobutane dimers and 6–4 photoproducts generated by UVB and most critical to carcinogenesis are removed by nucleotide excision repair (NER). NER has been extensively studied in bacteria, but studies in eucaryotes suggest that many similarities exist between the pathways in these two organisms. Two distinct subpathways of NER exist and can be selectively employed based on the type of DNA lesion and how rapidly it needs to be repaired. Transcription-coupled repair (TCR) rapidly repairs DNA regions that are transcriptionally active, while the global genome repair pathway (GGR) removes the bulky UV radiation-induced DNA lesions less quickly. These two subpathways differ from each other in the initial recognition steps: in TCR a stalled RNA polymerase II is the DNA damage signal for repair, while in GGR DNA damage recognition is through the protein complex XPC-hHR23B (reviewed by Hoeijmakers, 2001).

XPC represents one of seven complementation groups (XPA to XPG) associated with the autosomal recessive disease Xeroderma pigmentosum (XP) that are required for NER, and XP patients harboring homozygous deletions in XP genes have UVB-associated repair and replication deficiencies (Cleaver and Crowley, 2002). These individuals are hypersensitive to UV, and are at a 1000-fold higher risk of developing skin cancer, including melanoma, providing perhaps the strongest evidence for a connection between UV radiation and melanomagenesis (Kraemer, 1994). A number of excellent reviews have recently been written on the role of XP gene products and NER repair mechanisms (i.e. Hoeijmakers, 2001; Cleaver and Crowley, 2002; Matsumura and Ananthaswamy, 2002).

Islas and Hanawalt (1995) have identified different, context-dependent repair rates within the *MYC* proto-oncogene. When pyrimidine

dimers were induced in the promyelocytic cell line HL60 by UV irradiation and then analysed 18 h post-treatment, as many as 56% were removed in the *MYC* gene, which was being actively transcribed. In contrast, once the HL60 cells were differentiated, and *MYC* was no longer transcriptionally active, only 15% of the pyrimidine dimers were removed. Tornaletti and Pfeiffer (1994) showed that not only were there large differences in UV damage repair rates between the two strands of the TP53 gene in human skin fibroblasts, but that within the TP53 gene specific regions were repaired at a more rapid rate than others. These data suggest that differential rate repair might contribute to the generation of mutation hot spots identified within this important tumor suppressor gene. Interestingly, while TP53 seems to be a significant target of UV-mediated mutagenesis in squamous cell carcinoma, basal cell carcinoma and actinic keratoses, with a majority demonstrating UV signature lesions (Nataraj *et al.*, 1995), such mutations are very rare in melanoma.

Cellular responses to UV radiation

Eucaryotic cells have evolved highly intricate cellular responses to deal with the damage introduced by genotoxic agents such as UV radiation, so that mutations resulting from such damage are not fixed and perpetuated (see the reviews by Smith *et al.*, 2000; Decraene *et al.*, 2001; Kulms and Schwarz, 2002). The production of pyrimidine dimers and 6–4 photoadducts in cells by UVB radiation triggers classic DNA damage response pathways orchestrated by the tumor suppressor p53 (schematized in Figure 1). Cellular p53 is normally maintained at a low, steady-state level, but becomes rapidly stabilized upon exposure to genotoxic agents such as UV radiation or γ-irradiation. The cell then undergoes growth arrest designed to allow ample time to repair the damage to its genome. Re-entry into the cell cycle occurs only if DNA repair has been deemed successful; in the event of irreparable damage the cell can undergo apoptosis, avoiding the perpetuation of mutations in subsequent generations.

UV damage responses, cell cycle arrest and DNA repair and apoptosis are regulated by the accumulation and stabilization of p53, and cells that are deficient in p53 are sensitive to UV exposure and defective in UV repair (see reviews by Smith *et al.*, 2000; Decraene *et al.*, 2001). Moreover, p53-/- mice are extremely sensitive to the induction of tumors by UV radiation (Jiang *et al.*, 1999, 2001). This p53 response can be observed and has been extensively studied in both keratinocytes and fibroblasts; fewer studies have been carried out on normal melanocytes, representing a significant deficiency in the field. p53 induction in human skin can be observed in both the epidermis and dermis in response to UV exposure, and varies depending on the UV wavelength and dose. UVB exposure elicits an intense p53 response throughout the epidermis. In contrast, UVA induces a p53 response primarily in the basal layer of the epidermis, while UVC induces p53 only in the most superficial layers of the epidermis (Campbell *et al.*, 1993). In this section, we discuss general cellular responses to UV radiation, while attempting to focus on pathways most relevant to melanocytes and melanomagenesis (refer to Figure 1).

UV-mediated cell cycle arrest and re-entry

One of the first consequences of p53 induction in response to UV-generated DNA damage is G1 cell cycle arrest, mediated by the cyclin-dependent kinase (Cdk) inhibitor $p21^{waf1}$, whose transcription is directly induced by p53. Cells deficient in $p21^{waf1}$ are unable to undergo growth arrest in response to DNA damage and become susceptible to apoptosis (see below). Normal G1 arrest is necessary to repair DNA damage before the cycling cell proceeds into S phase, and previous studies have illustrated that half of all pyrimidine dimer reductions take place in keratinocytes within the first few hours following UV treatment (Liu *et al.*, 1982; Jung, 1986). UVB-induced G1 arrest has also been demonstrated in cultured human melanocytes and correlated with the prolonged expression of

both p53 and $p21^{waf1}$ (Medrano *et al.*, 1995).

The ATM-Rad3-related protein ATR has been implicated in cell cycle checkpoint control as well (Wright *et al.*, 1998), and in fibroblasts phosphorylates p53 in response to UV and other DNA damage (Tibbetts *et al.*, 1999). Recently, it was shown that ATR could preferentially bind to UV-damaged DNA with a resulting increase in its kinase activity, suggesting that ATR may act as an initial DNA damage sensor (Unsal-Kacmaz *et al.*, 2002).

Cells can also arrest in the G2 phase of the cell cycle, a regulatory mechanism involving a number of p53-dependent factors including 14-3-3$_\sigma$ and the growth-arrest and DNA damage-inducible gene Gadd45a (Chan *et al.*, 1999; Hwang *et al.*, 1999; Amundson *et al.*, 2000; Jin *et al.*, 2000; Yang *et al.*, 2000). Interestingly, Gadd45 can be upregulated by UV exposure in a p53-independent fashion through the transcriptional factors Oct-1 and NF-YA (Jin *et al.*, 2000; Takahashi *et al.*, 2001). p53-independent G2 arrest in response to UV also involves a p38 kinase-mediated block in the activation of the mitotic Cdk complexes by cdc25 (Herzinger *et al.*, 1995; Gabrielli *et al.* 1997; Bulavin *et al.*, 2001; Pavey *et al.*, 2001). Recent studies making use of short-term, whole-organ skin cultures have confirmed that basal and suprabasal layer melanocytes and keratinocytes undergo G2 cell cycle arrest in response to suberythemal doses of UV radiation (Pavey *et al.*, 2001). While this G2 arrest does not appear to involve p53, it is associated with increased expression of the cell cycle inhibitor p16INK4a.

A key question that has not been adequately addressed concerns the nature of the molecular mechanisms by which DNA-damaged cells abandon growth arrest and re-enter the cell cycle. Unique to cells that have sustained UV damage response is the 'pseudo growth response', not observed following exposure to other genotoxic agents such as γ irradiation. This response involves dramatic transcriptional induction of immediate-early mitogen-regulated genes including c-*fos* and

c-*jun* (Holbrook and Fornace, 1991; Karin, 1995). Such a response would appear paradoxical in view of the fact that UV-treated cells undergo p53-driven cell cycle arrest, but reflects the ultimate necessity of reinitiating cell growth following successful damage repair. The rapid UV-mediated induction of c-*jun*, involving activation of JNK through MAPK signaling pathways, occurs through interactions with the cell membrane rather than a direct consequence of DNA damage. Recently, Shaulian *et al.* (2000) showed that c-*jun* promotes cell cycle re-entry in mouse fibroblasts by inhibiting the association of p53 to the $p21^{waf1}$ promoter. Such studies suggest an important role for c-*jun* in releasing cells from G1 arrest after DNA repair is complete, thus preventing prolonged $p21^{waf1}$ cell cycle arrest that could trigger cellular senescence. Although it is not clear if this mechanism applies to mature melanocytes, which are much less prolific than fibroblasts, it may be more relevant in melanocyte progenitors, or melanoblasts, more commonly found in younger skin. It is known that the upregulation of α-MSH and MC1R in melanocytes by UV stimulates cAMP production, facilitating re-entry into the cell cycle as well as pigment production (reviewed by Suzuki *et al.*, 1999; see below).

DNA repair pathways

A number of genes transcriptionally activated by p53 also help regulate DNA repair pathways following UV damage (reviewed by Smith and Seo, 2002). Two of these effector genes, damaged DNA binding 2 (DDB2 (XPE)) and XPC, are XP genes involved in the recognition of DNA damage in the GGR subpathway of NER (Hwang *et al.*, 1999; Amundson *et al.*, 2000, 2002; Adimoolam and Ford, 2002). Recently, the tumor suppressor BRCA1 was reported to be required for p53-dependent upregulation of DDB2 (Takimoto *et al.*, 2002). In addition to its role in activation of the G2/M checkpoint, p53-activated Gadd45a is also involved in chromatin relaxation and UV damage recognition (Carrier *et al.*, 1999), and is required for normal NER function (Smith *et*

al., 2000; Hollander *et al.*, 2001). Studies carried out on the endogenous copy of the dihydrofolate reductase (DHFR) gene in Li–Fraumeni fibroblasts, which are deficient in p53, demonstrated that the transcribed strand remained unaffected by the absence of p53, whereas repair of the nontranscribed strand was adversely affected (Ford and Hanawalt, 1995; Wang *et al.*, 1995). These data indicate that p53 plays an essential role in GGR, but not TCR. Wang and colleagues have also suggested that p53 may interact directly with and modulate TFIIH, a component of the NER machinery (Wang *et al.*, 1995; Smith *et al.*, 2000).

Resistance to UV-induced apoptosis

Melanomas are notoriously chemoresistant, suggesting that information gleaned from in-depth studies of apoptotic pathways in melanocytes relative to other cell types may uncover clinically relevant information (e.g., see the review by Hersey and Zhang, 2001). Most cells that are subjected to irreparable harm and become too damaged to be propagated (i.e., as a consequence of high doses of UV radiation) undergo apoptosis (Decraene *et al.*, 2001; Kulms and Schwarz, 2002). This is a process that is highly characteristic of keratinocytes, and less dramatic in melanocytes. As for other UV response pathways, apoptosis is by and large mediated by p53, and p53-deficient mice exhibit a decrease in epidermal apoptotic nuclei compared to wild-type mice after UV treatment (Ziegler *et al.*, 1994). p53-mediated apoptosis is centered around transcriptional activation of Bax, a proapoptotic member of the Bcl-2 family (Oltvai *et al.*, 1993). The apoptotic action of Bax is inhibited by its dimerization with Bcl-2, so the ratio of Bcl-2 and Bax determines if a cell will be targeted for apoptosis. Bcl-2 is produced at high levels in melanocytes, which may help explain their relative resistance to apoptosis following extensive DNA damage (Klein-Parker *et al.*, 1994; van den Oord *et al.*, 1994; Plettenberg *et al.*, 1995). In fact, both Bcl-2 and its regulator Microphthalmia-associated transcription factor

(Mitf) have been shown to be critical to melanocyte survival, as judged by the depletion of melanocytes in mice deficient in either of these genes (Lerner *et al.*, 1986; Nakayama *et al.*, 1994; Kamada *et al.*, 1995; Yamamura *et al.*, 1996; McGill *et al.*, 2002).

The cellular decision on whether to undergo apoptosis or cell cycle arrest and repair may be influenced by the dose of UV to which cells are exposed. p53-driven induction of $p21^{waf1}$ was observed in mouse fibroblasts exposed to low UVB doses, but upon exposure to higher doses Bax and not $p21^{waf1}$ was induced, leading to apoptosis (Reinke and Lozano, 1997; Li and Ho, 1998). It is assumed that surviving mutant melanocytes serve to maintain the integrity of the skin's sole source of melanin, thereby ensuring uninterrupted protection against subsequent UV radiation (Gilchrest *et al.*, 1999).

UV-induced melanogenesis

Perhaps the most obvious effect of UV radiation on melanocytes is the stimulation of melanin production (Gilchrest and Eller, 1999). UV facilitates melanocyte differentiation through a number of pathways. UV induces the production of active α-MSH and its receptor, MC1R (Bolognia *et al.*, 1989; Chakraborty *et al.*, 1995, 1996; Funasaka *et al.*, 1998; Suzuki *et al.*, 1999). It has been reported that MC1R stimulation induces adenylate cyclase, leading to cAMP production, protein kinase A (PKA) activation, Mitf upregulation, tyrosinase and TRP1 upregulation, and ultimately enhanced melanin synthesis (Hearing and Tsukamoto, 1991; Abdel-Malek *et al.*, 1995; Ao *et al.*, 1998; Busca and Ballotti, 2000). Recently, BRAF was shown to be an activational target of cAMP, linking MC1R with ERK signaling (Busca *et al.*, 2000), and MAPK was reported to phosphorylate and activate Microphthalmia (Hemesath *et al.*, 1998), a basic/helix–loop–helix/leucine zipper factor required for pigment cell development (Hodgkinson *et al.*, 1993). These studies forge a potential link between BRAF activity and differentiation. The role of RAS/BRAF in

regulating vital melanocytic activities may be significant, particularly in light of the recent discovery that 66% of cultured and primary melanoma cells harbor activating BRAF mutations (Davies *et al.*, 2002).

Interestingly, tyrosinase and TRP1, both critical factors in melanin synthesis, have also been implicated as downstream effectors of p53. Tyrosinase can be induced after UV radiation in a p53-dependent manner (Nylander *et al.*, 2000; Khlgatian *et al.*, 2002), and tyrosinase activity is increased in G2-arrested melanoma cells, as is α-MSH expression (Wong *et al.*, 1974; McLane and Pawelek, 1988; Chakraborty *et al.*, 1999). These results support a profound role for p53 in the response of melanocytes to UV damage, permitting cells to pause in the cell cycle to repair or die, yet simultaneously encouraging melanin synthesis and increased differentiation. The resulting enhancement in melanin synthesis may provide a further level of protection against UV damage (see reviews by Thody and Graham, 1998; Suzuki *et al.*, 1999).

UV-induced proliferation and the role of growth factor receptors

It has been suggested that UV acts as an independent melanocyte mitogen (Libow *et al.*, 1988), and in fact UV can directly activate cell surface growth factor receptors in a ligand-independent fashion, leading to clustering and internalization (Sachsenmaier *et al.*, 1994; Knebel *et al.*, 1996; Rosette and Karin, 1996). A mechanism that has been proposed for this receptor activation is oxidative stress-mediated protein tyrosine phosphatase inhibition (Gross *et al.*, 1999). UV-activated growth factor receptors, including receptor tyrosine kinases (RTKs), appear to become fully functional as judged by the rapid stimulation of pathways such as RAS/RAF (Devary *et al.*, 1992; Radler-Pohl *et al.*, 1993), establishing the potential to evoke a proliferative response. As discussed above with respect to pigmentation, these pathways take on added significance considering that the majority of melanomas harbor either RAS or

BRAF mutations (Davies *et al.*, 2002). UV activation of these same receptors could also trigger other tumor-promoting activities, such as survival through the PI3-kinase/AKT pathway (Mildner *et al.*, 1999; Wan *et al.*, 2001; Xiao *et al.*, 2001).

It is worth noting that activation of MC1R by UV and/or α-MSH can stimulate signaling through both the PKA and MAPK pathways, which could potentially induce melanocytic growth (Abdel-Malek *et al.*, 1995, 1999). However, there are conflicting data on the effect of α-MSH on the growth of melanocytic cells, which may be relevant only to cells in culture (see the review by Thody, 1999). Moreover, UVB is known to induce expression of the cell cycle inhibitor p16INK4a (Pavey *et al.*, 2001), an effect that is potentiated by α-MSH (Pavey and Gabrielli, 2002).

An exciting and largely unexplored area of research concerns the stimulation of melanocytes through UV-mediated upregulation of growth factors, such as endothelin-1 and bFGF, originating from nonmelanocyte cell types (Archambault *et al.*, 1995; Tada *et al.*, 1998). MC1R expression is known to be regulated by paracrine as well as autocrine factors that are induced in the epidermis in response to sun exposure (see the review by Abdel-Malek *et al.*, 1999). These UV-mediated responses would establish potent paracrine signaling loops in the skin, facilitating survival and growth of normal and perhaps damaged melanocytes. Although complex, it is anticipated that analysis of the mechanisms that drive the biological and physiological responses of normal melanocytes to UV radiation may elucidate how these cells undergo malignant transformation, and the risk factors associated with this process. As a case in point, Berking and Herlyn (2001) have shown that paracrine RTK stimulation established through forced overexpression of bFGF in dermal fibroblasts can induce melanomagenesis in human skin xenografts when combined with UV irradiation (see below).

Melanoma models

Sun exposure is widely regarded as the critical environmental risk factor for cutaneous malignant melanoma, which arises as a consequence of deleterious interactions between UV radiation and the melanocyte genome. Although great strides are being made in understanding the underlying genetic basis of melanoma (see other reviews in this issue), fundamental questions concerning UV radiation and the mechanisms by which it operates remain unresolved, compromising efforts to develop effective sun protection strategies and antimelanoma therapy. These circumstances have been fueled, at least in part, by the lack of a suitable genetically tractable, UV-dependent animal model for human melanoma. Although a number of animal melanoma models have now been described (Kusewitt and Ley, 1996; Chin *et al.*, 1998; Ley, 2002), the histopathological appearance and graded progression of the arising melanocytic malignancies have been, for the most part, distinct from human melanoma. In a subset of models, melanoma has been successfully induced by exposure to carcinogens; however, most studies employ the initiator DMBA, an agent of unknown environmental relevance with respect to human disease. The majority of described melanoma model systems have not demonstrated appropriate responsiveness to UV exposure. For example, the Syrian hamster, guinea-pig and Sinclair swine represent promising animal models for melanoma, but show no UV responsiveness and are not discussed further in this review. In this section, we review the UV-responsive animal models that have been generated, describe recent significant progress in the field, and discuss prospects for future advances.

Xiphophorus hybrid fish

One of the earliest animal models of melanoma was developed in the Central American freshwater fish Xiphophorus. Xiphophorus in the wild does not develop melanoma, but hybrid crosses generated by breeding different

species of the genus can be prone to both spontaneous as well as UV-induced melanoma (Anders *et al.*, 1984; Schartl *et al.*, 1995). Extensive genetic analysis of melanoma response in Xiphophorus has revealed the presence of the Tu (Tumor) locus, consisting of a series of genes closely linked on the sex chromosomes. These allelic genes act as dominant oncogenes and are suppressed by a series of regulatory R genes that act to negate Tu-induced melanoma development. The R genes are fully functional when present in two copies and, depending on how many R genes are present in the hybrid Xiphophorus, the Tu genes may generate a range of phenotypes including black spotting, benign melanoma, and highly invasive melanoma (Anders *et al.*, 1984; Kusewitt and Ley, 1996; Bardeesy *et al.*, 2000). The R genes appear to exert their suppressive function by altering the ability of melanocytes to differentiate. For example, the Diff (differentiation) R gene acts to promote the differentiation of melanoblasts, while the g (golden) R gene, when present in a homozygous state, acts to prevent the development of either normal or neoplastic dermal macromelanophores. Notably, a Xiphophorus homolog of human INK4a maps to the R locus (Nairn *et al.*, 1996; Kazianis *et al.*, 1998). One of the Tu genes, Xmrk, has proven to be of particular interest. Xmrk encodes a membrane-bound receptor tyrosine kinase related to epidermal growth factor receptor (EGFR) (Wittbrodt *et al.*, 1989, 1992; Malitschek *et al.*, 1995). All Xiphophorus species contain one copy of the Xmrk proto-oncogene, whereas the tumor-prone species carries an additional mutated copy that appears to be responsible for melanoma formation in hybrid Xiphophorus. Transfection of Xmrk into the NIH 3T3 cell line has proven to be highly oncogenic, and if the Xmrk gene is deleted, fish do not develop black spots and are not susceptible to melanoma (Kusewitt and Ley, 1996).

Exposure of some Xiphophorus hybrids to UV radiation of wavelengths between 290 and 400 nm markedly enhances melanomagenesis (Setlow *et al.*, 1989, 1993; Setlow and

Woodhead, 1994). This Xiphophorus hybrid system, which is amenable to genetic manipulation and demonstrates full progression from black spots to metastatic disease, has provided a number of notable insights. Removal of UV-induced pyrimidine dimers by exposure to photoreactivating light greatly reduces tumor formation in Xiphophorus hybrids, implicating UV-induced DNA damage in melanomagenesis. Further studies by Setlow and colleagues using different UV wavebands have suggested a role for UVA radiation in the formation of melanoma in Xiphophorus (Setlow *et al.*, 1989; Kusewitt and Ley, 1996). However, the Xiphophorus hybrid fish system is ultimately limited by its evolutionary distance from mammals. Tumors do not develop from typical melanocytes, and do not resemble human melanomas.

South American Opossum

Like the Xiphophorus hybrid fish, the South American Opossum *Monodelphis domestica* has also been used as a model for melanoma (Kusewitt and Ley, 1996; Bardeesy *et al.*, 2000; Ley, 2002). Unlike the fish system, the genetics in this animal has been poorly defined. However, the opossum has been used extensively in photobiology studies because of the ease with which the repair of UV-induced pyrimidine dimers can be manipulated. This animal uses the photoreactivity pathway to repair these dimers (Applegate and Ley, 1987; Ley, 1987; Ley *et al.*, 1988). The photolyase enzyme recognizes and binds UV-induced pyrimidine dimers and then uses the absorbed energy of visible light to drive their monomerization. Exposure to photoreactivating light after DNA damage induced by suberythemal UV radiation can lead to the removal of 80–90% of pyrimidine dimers in the skin. These studies have been useful in assessing the role of UV-induced damage in skin tumors, erythema and edema, as well as in the disappearance of epidermal Langerhans cells. Melanoma in the opossum rarely occurs spontaneously, but can be induced by chronic exposure to suberythemal UV radiation, making it one of the very few

nontransgenic animals in which melanoma can be induced by UV alone. Contrary to the Xiphophorus model, exposure to UVA was only able to induce melanocytic hyperplasia in the opossum, rather than malignant melanoma (Ley, 2001). The South American Opossum is limited by its genetic obscurity, and the fact that the melanocytic tumors that arise are, unlike human melanoma, solely dermal in origin and metastasize infrequently.

Genetically engineered mouse models

The mouse currently represents the best available animal model for cutaneous malignant melanoma. The genetics of the mouse is well characterized and can be easily manipulated. Moreover, the murine immune system is fairly well understood, and numerous inbred and immunodeficient strains are available for experimental transplantation studies. Spontaneous melanomas are exceedingly rare in wild-type mice, but can be induced in some cases with DMBA and other agents. The resulting melanomas, which develop in the dermis and rarely metastasize, are thought to be derived from dermal melanocytes or melanocytes of the hair bulb, or possibly from a perifollicular melanocyte network. The incidence of chemically induced melanoma in mice can be enhanced by treatment with tumor-promoting agents such as croton oil. Studies dating back to 1963 have demonstrated that UV radiation could be used in combination with chemical treatment to induce melanoma in mice, but could not act as a complete carcinogen (Epstein *et al.*, 1967; Romerdahl *et al.*, 1989; Husain *et al.*, 1991).

The advent of genetic engineering and other recent technological advances have catapulted the mouse to the forefront of human cancer modeling. Currently, a number of melanoma-prone transgenic lines of mice have been described, providing critical insights into genetic mechanisms that predispose melanocytes to neoplastic transformation. These models (reviewed in greater detail elsewhere in this issue) incorporate singly or in combination: inactivation of ink4a/arf, p53 or

PTEN, and aberrant expression of activated H-Ras, Cdk4 and RTKs or their ligands, validating the role of a number of key pathways in melanomagenesis. Here we will focus on the UV-responsive mouse melanoma models.

An early UV-responsive mouse melanoma model was described by Kelsall and Mintz (1998)and was generated by expressing the SV40 early region (encoding both the large and small T antigens) under the direction of the melanocyte-specific tyrosinase promoter. The majority of the resulting lines of mice developed ocular melanoma. However, one low susceptibility line could be coaxed to develop cutaneous melanoma in approximately 20% of treated animals through multiple rounds of neonatal exposure to UVB radiation. Notable as an early success in inducing cutaneous melanoma with UV radiation alone, this model suffers from the multifaceted effects of SV40 T antigens, limiting the ability to analyse relevant pathways. However, it was discovered that melanocytes derived from these transgenic mice acquired malignant properties after a single *in vitro* exposure to UVB radiation (Larue *et al.*, 1992). In another series of studies, melanomas did not develop spontaneously in transgenic mice in which expression of H-RAS^{V12G} was targeted to melanocytes using the tyrosinase promoter, but could be induced by DMBA and to a lesser extent by UV radiation (Broome Powell *et al.*, 1999). Interestingly, melanomas arising after such treatment were characterized by deletions on chromosome 4, leading to diminished expression of p16ink4a, p19arf and p15ink4b (Gause *et al.*, 1997). This mutational event is reminiscent of that occurring in human melanoma.

A role for perturbation of RTK signaling in the development of melanoma has been long appreciated. The involvement of the EGFR-like Xmrk gene in melanoma development in Xiphophorus has already been alluded to (see above). RTKs also play a role in the complex cellular signaling circuitry critical to the development and function of mammalian melanocytes, making them a logical target in

melanoma pathogenesis. Scott *et al.* (1991) presented immunohistochemical evidence that inappropriate expression of both bFGF and FGFR can already be detected in dysplastic nevi, considered by many to be premalignant melanoma precursor lesions (Tucker *et al.*, 1983; Landi *et al.*, 2002), and expression of antisense bFGF or FGFR has been shown to have anti-melanoma properties (Wang and Becker, 1997). Extensive analysis of human melanoma has implicated numerous RTKs in melanomagenesis, including the EGFR and hepatocyte growth factor/scatter factor (HGF/SF) receptor, c-MET (Albino, 1992; Shih and Herlyn, 1994; Halaban, 1996; Chin *et al.*, 1998; Bardeesy *et al.*, 2000), and the creation of autocrine loops through coexpression of both these receptors and their cognate ligands has come to be considered a hallmark of melanoma. Significantly, gains in copy number for regions of chromosome 7 encoding both c-MET and EGFR occur in melanoma (Wiltshire *et al.*, 1995; Bastian *et al.*, 1998). Several transgenic mouse studies have validated RTKs as melanoma oncogenes. Transgenic mice expressing an activated form of the RTK Ret by virtue of a mouse metallothionein promoter developed melanocytic tumors, which could be further induced to metastatic progression by exposure to intense UV radiation (Kato *et al.*, 1998, 2000). Metallothionein-driven expression of HGF/SF, a multifunctional cytokine capable of stimulating a variety of cellular behaviors associated with tumorigenesis including growth, motility and invasiveness (reviewed by Jeffers *et al.*, 1996; Comoglio and Boccaccio, 2001), also induced the appearance of cutaneous melanoma with metastatic potential in aged transgenic mice (Takayama *et al.*, 1997; Otsuka *et al.*, 1998). These mice, and indeed all mouse models that have been described, develop dermal melanomas with little histopathological resemblance to their human counterpart. However, a notable exception was uncovered through exposure of HGF/SF transgenic mouse to UV radiation.

Melanocytes in HGF/SF transgenic mice are found in the epidermis, dermis and

epidermal–dermal junction, distinct from wild-type mouse and more akin to human skin (Otsuka *et al.*, 1998; Noonan *et al.*, 2000). When adult mice of this transgenic line were subjected to chronic exposure of suberythemal doses of UV radiation, squamous cell tumors and fibrosarcomas were induced rather than melanoma (Noonan *et al.*, 2000). In a subsequent experiment, HGF/SF neonates were exposed to a single erythemal dose of UV radiation corresponding to less than 3 h of midsummer, midlatitude sunlight. In striking contrast to the chronic treatment of adults, this single neonatal treatment was found to be necessary and sufficient to induce melanoma in HGF/SF transgenic mice after a relatively short latent period and with a high incidence (Noonan *et al.*, 2001). The addition of a second burning dose in young adults did not alter the latency or frequency of melanoma in these mice, but did significantly enhance the multiplicity, with most treated animals exhibiting more than one melanocytic lesion. These results, schematized in Figure 2, offer the first experimental support for previous epidemiological studies implicating childhood sunburn as a critical melanoma risk factor (Holman *et al.*, 1983; Whiteman *et al.*, 2001), and suggest that additional exposures to burning doses of UV radiation may promote melanomagenesis.

Unexpectedly, tumors that arose in the HGF/SF transgenic mouse as a consequence of erythemal neonatal UV radiation bore a remarkable histopathological resemblance to human melanoma, demonstrating staged progression from premalignant dysplastic foci, through radial and vertical growth phases, and culminating in the metastatic phenotype (Noonan *et al.*, 2001). Primary tumors frequently had epidermal involvement, or junctional activity, including the so-called pagetoid spreading. Moreover, similarities were noted at the molecular pathogenetic level, including acquisition of RTK autocrine signaling loops, lack of p53 mutations and loss of ink4a/arf (Recio *et al.*, 2002). The significance of the latter was confirmed by placing the HGF/SF transgene on an

Ink4a/Arf-deficient background, significantly accelerating melanomagenesis following neonatal UV irradiation (Recio *et al.*, 2002).

Human skin xenograft models

The genetically engineered mouse models currently available will undoubtedly provide tremendous insight into the contribution of UV radiation and genetics to melanoma, and to the underlying mechanisms by which they operate and interact. The wealth of genetic knowledge and the ease by which it can be manipulated make the mouse an excellent experimental model system. However, genetic alterations and environmental insults in mice do not always operate as in humans (see the review by Van Dyke and Jacks, 2002). To overcome these limitations, Herlyn and colleagues employed mice bearing human skin as subjects for UV carcinogenesis studies (Berking and Herlyn, 2001). UVB treatment of immunodeficient mice engrafted with human newborn foreskin produced melanocytic hyperplasia and, in combination with DMBA initiation, infrequently induced nodular melanoma (Atillasoy *et al.*, 1998). In subsequent experiments, similar xenografts of adult human skin failed to develop melanocytic lesions when treated with UV radiation with or without DMBA, instead spawning actinic keratoses (Berking *et al.*, 2002). These data indicate that melanocytes from adult human skin are far less susceptible to melanomagenesis than those in newborn skin, a result that is in complete concordance with the aforementioned data obtained from UV-treated HGF/SF transgenic mice (Noonan *et al.*, 2000, 2001). It is likely that the susceptible cellular target specific to newborn skin is the melanocyte progenitor, which is present as a significantly higher proportion of the melanocytic population in young mice (Hirobe, 1984).

Human foreskin grafts have also been used to determine the contribution of constitutive RTK signaling in UV-induced melanomagenesis. Human foreskin grafted onto SCID mice and infected with bFGF-expressing adenovirus developed skin hyperpigmentation and

melanocyte hyperplasia within 3 weeks, but not melanoma. However, exposure of this bFGF-expressing human skin to UVB radiation resulted in the development of a lesion resembling the lentiginous form of malignant melanoma (Berking and Herlyn, 2001). Most recently, Herlyn and colleagues found that melanoma could be induced to appear in UVB-irradiated human foreskin with a higher incidence and a shorter latency through forced expression of multiple RTK growth factors (M Herlyn, personal communication). This model, again like the UV-treated HGF/SF transgenic mouse, lends support to the notion that disruption of RTK signaling pathways in conjunction with UV irradiation strongly promotes melanomagenesis. These emerging data suggest that transgenic and human skin xenograft models represent compelling, complementary approaches, the sum of which should provide significant advances in our understanding of pathogenesis and our ability to successfully treat melanoma.

Concluding perspective

This is an extremely exciting period for melanoma research. Seminal discoveries are being made continually and on a broad front, greatly enhancing our knowledge base at both the basic and clinical level. Some of this success can be attributed to recent advances in the development of UV-responsive animal models of cutaneous malignant melanoma. The genetic diversity provided by transgenic mice, and the relevance afforded by mice bearing human skin xenografts constitutes a powerful combination of experimental tools. The availability of these *in vivo* models takes on special significance in studies directed toward elucidating the mechanism by which genetic and environmental factors interact in melanomagenesis, and when employed as agents for preclinical trials. Melanoma researchers look eagerly toward the future with the hope and expectation that these recent advances will lead to successful strategies for the prevention, and more effective therapy for the treatment, of this rapidly escalating malignancy.

Acknowledgements

We thank Drs Dot Bennett, Al Fornace, Vince Hearing, Meenhard Herlyn, Bill Pavan, Pam Pollock and Juan Recio for helpful comments and useful discussions.

References

Abdel-Malek Z, Suzuki I, Tada A, Im S and Akcali C. (1999). *Ann. NY Acad. Sci.*, **885**, 117–133.

Abdel-Malek Z, Swope VB, Suzuki I, Akcali C, Harriger MD, Boyce ST, Urabe K and Hearing VJ. (1995). *Proc. Natl. Acad. Sci. USA*, **92**, 1789–1793.

Adimoolam S and Ford JM. (2002). *Proc. Natl. Acad. Sci. USA*, **19**, 19.

Albino AP. (1992). *Pigment Cell Res.*, (Suppl), **2** 199–218.

Amstad P, Hussain SP and Cerutti P. (1994). *Mol. Carcinog.*, **10**, 181–188.

Amundson SA, Do KT, Shahab S, Bittner M, Meltzer P, Trent J and Fornace Jr AJ. (2000). *Radiat. Res.*, **154**, 342–346.

Amundson SA, Patterson A, Do KT and Fornace Jr AJ. (2002). *Cancer Biol. Ther.*, **1**, 145–149.

Anders F, Schartl M, Barnekow A and Anders A. (1984). *Adv. Cancer Res.*, **42**, 191–275.

Ao Y, Park HY, Olaizola-Horn S and Gilchrest BA. (1998). *Exp. Cell Res.*, **244**, 117–124. PubMed

Applegate LA and Ley RD. (1987). *Photochem. Photobiol.*, **45**, 241–245.

Archambault M, Yaar M and Gilchrest BA. (1995). *J. Invest. Dermatol.*, **104**, 859–867.

Armstrong BK. (1988). *J. Dermatol. Surg. Oncol.*, **14**, 835–849.

Armstrong BK and Kricker A. (1994). *Cancer Surv.*, **20**, 219–240.

Armstrong BK and Kricker A. (1995). *Dermatol Clin.*, **13**, 583–594.

Armstrong BK, Kricker A and English DR. (1997). *Australas. J. Dermatol.*, **38**(Suppl 1), S1–S6.

Atillasoy ES, Seykora JT, Soballe PW, Elenitsas R, Nesbit M, Elder DE, Montone KT, Sauter E and Herlyn M. (1998). *Am. J. Pathol.*, **152**, 1179–1186. PubMed

Autier P and Dore JF. (1998). *Int. J. Cancer*, **77**, 533–537.

Bardeesy N, Wong KK, DePinho RA and Chin L. (2000). *Adv. Cancer Res.*, **79**, 123–156.

Barnhill RL and Mihm Jr MC. (1993). *Semin. Diagn. Pathol.*, **10**, 47–75.

Bastian BC, LeBoit PE, Hamm H, Brocker EB and Pinkel D. (1998). *Cancer Res.*, **58**, 2170–2175. PubMed

Bennett JP and Hall P. (1994). *Ann. R. Coll. Surg. Engl.*, **76**, 373–380.

Berking C and Herlyn M. (2001). *Histol. Histopathol.*, **16**, 669–674.

Berking C, Takemoto R, Binder RL, Hartman SM, Ruiter DJ, Gallagher PM, Lessin SR and Herlyn M. (2002). *Carcinogenesis*, **23**, 181–187. Article PubMed

Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B, Chompret A, Ghiorzo P, Gruis N, Hansson J, Harland M, Hayward N, Holland EA, Mann GJ, Mantelli M, Nancarrow D, Platz A and Tucker MA. (2002). *J. Natl. Cancer Inst.*, **94**, 894–903. Article PubMed

Black HS, deGruijl FR, Forbes PD, Cleaver JE, Ananthaswamy HN, deFabo EC, Ullrich SE and Tyrrell RM. (1997). *J. Photochem. Photobiol. B*, **40**, 29–47.

Bolognia J, Murray M and Pawelek J. (1989). *J. Invest. Dermatol.*, **92**, 651–656.

Box NF, Wyeth JR, O'Gorman LE, Martin NG and Sturm RA. (1997). *Hum Mol Genet*, **6**, 1891–1897. Article PubMed

Broome Powell M, Gause PR, Hyman P, Gregus J, Lluria-Prevatt M, Nagle R and Bowden GT. (1999). *Carcinogenesis*, **20**, 1747–1753.

Bruls WA, van Weelden H and van der Leun JC. (1984). *Photochem. Photobiol.*, **39**, 63–67.

Bulavin DV, Higashimoto Y, Popoff IJ, Gaarde WA, Basrur V, Potapova O, Appella E and Fornace Jr AJ. (2001). *Nature*, **411**, 102–107. Article PubMed

Busca R, Abbe P, Mantoux F, Aberdam E, Peyssonnaux C, Eychene A, Ortonne JP and Ballotti R. (2000). *EMBO J.*, **19**, 2900–2910. Article PubMed

Busca R and Ballotti R. (2000). *Pigment Cell Res.*, **13**, 60–69.

Cadet J, Berger M, Douki T, Morin B, Raoul S,

Ravanat JL and Spinelli S. (1997). *Biol. Chem.*, **378**, 1275–1286. PubMed

Campbell C, Quinn AG, Angus B and Rees JL. (1993). *Br. J. Dermatol.*, **129**, 235–241.

Carrier F, Georgel PT, Pourquier P, Blake M, Kontny HU, Antinore MJ, Gariboldi M, Myers TG, Weinstein JN, Pommier Y and Fornace Jr AJ. (1999). *Mol. Cell Biol.*, **19**, 1673–1685. PubMed

Chakraborty AK, Funasaka Y, Slominski A, Bolognia J, Sodi S, Ichihashi M and Pawelek JM. (1999). *Ann. NY Acad. Sci.*, **885**, 100–116.

Chakraborty AK, Funasaka Y, Slominski A, Ermak G, Hwang J, Pawelek JM and Ichihashi M. (1996). *Biochim. Biophys. Acta*, **1313**, 130–138. PubMed

Chakraborty A, Slominski A, Ermak G, Hwang J and Pawelek J. (1995). *J. Invest. Dermatol.*, **105**, 655–659.

Chan TA, Hermeking H, Lengauer C, Kinzler KW and Vogelstein B. (1999). *Nature*, **401**, 616–620. Article PubMed

Chhajlani V and Wikberg JE. (1992). *FEBS Lett.*, **309**, 417–420.

Chin L, Merlino G and DePinho RA. (1998). *Genes Dev.*, **12**, 3467–3481. PubMed

Cleaver JE and Crowley E. (2002). *Front. Biosci.*, **7**, d1024–d1043.

Comoglio PM and Boccaccio C. (2001). *Semin. Cancer Biol.*, **11**, 153–165. Article PubMed

Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR and Futreal PA. (2002). *Nature*, **417**, 949–954. Article PubMed

de Gruijl FR. (1999). *Eur. J. Cancer*, **35**, 2003–2009.

Decraene D, Agostinis P, Pupe A, de Haes P and Garmyn M. (2001). *J. Photochem. Photobiol. B*, **63**, 78–83.

Devary Y, Gottlieb RA, Smeal T and Karin M. (1992). *Cell*, **71**, 1081–1091. PubMed

Elder DE. (1987). *Pathobiology of Malignant Melanoma*. Karger, Basel: New York.

Elwood JM and Jopson J. (1997). *Int. J. Cancer*, **73**, 198–203. PubMed

Epstein JH, Epstein WL and Nakai T. (1967). *J. Natl. Cancer Inst.*, **38**, 19–30.

Evans RD, Kopf AW, Lew RA, Rigel DS, Bart RS, Friedman RJ and Rivers JK. (1988). *J. Dermatol. Surg. Oncol.*, **14**, 393–408.

Ford JM and Hanawalt PC. (1995). *Proc. Natl. Acad. Sci. USA*, **92**, 8876–8880. PubMed

Funasaka Y, Chakraborty AK, Hayashi Y, Komoto M, Ohashi A, Nagahama M, Inoue Y, Pawelek J and Ichihashi M. (1998). *Br. J. Dermatol.*, **139**, 216–224.

Gabrielli BG, Clark JM, McCormack AK and Ellem KA. (1997). *Oncogene*, **15**, 749–758.

Garbe C, Buttner P, Weiss J, Soyer HP, Stocker U, Kruger S, Roser M, Weckbecker J, Panizzon R, Bahmer F and *et al.* (1994). *J. Invest. Dermatol.*, **102**, 695–699.

Gause PR, Lluria-Prevatt M, Keith 0WN, Balmain A, Linardopolous S, Warneke J and Powell MB. (1997). *Mol. Carcinog.*, **20**, 78–87.

Gilchrest BA and Eller MS. (1999). *J. Invest. Dermatol. Symp. Proc.*, **4**, 35–40.

Gilchrest BA, Eller MS, Geller AC and Yaar M. (1999). *N. Engl. J. Med.*, **340**, 1341–1348. PubMed

Goldstein AM and Tucker MA. (2001). *Arch. Dermatol.*, **137**, 1493–1496.

Gross S, Knebel A, Tenev T, Neininger A, Gaestel M, Herrlich P and Bohmer FD. (1999). *J. Biol. Chem.*, **274**, 26378–26386.

Halaban R. (1996). *Semin. Oncol.*, **23**, 673–681.

Haluska FG and Hodi FS. (1998). *J. Clin. Oncol.*, **16**, 670–682. PubMed

Healy E, Flannagan N, Ray A, Todd C, Jackson IJ, Matthews JN, Birch-Machin MA and Rees JL. (2000). *Lancet*, **355**, 1072–1073.

Hearing VJ. (1999). *J. Invest. Dermatol. Symp. Proc.*, **4**, 24–28.

Hearing VJ and Tsukamoto K. (1991). *FASEB J.*, **5**, 2902–2909.

Hemesath TJ, Price ER, Takemoto C, Badalian T and Fisher DE. (1998). *Nature*, **391**, 298–301. Article PubMed

Hersey P and Zhang XD. (2001). *Nat. Rev. Cancer*, **1**, 142–150. Article PubMed

Herzinger T, Funk JO, Hillmer K, Eick D, Wolf DA and Kind P. (1995). *Oncogene*, **11**, 2151–2156. PubMed

Hirobe T. (1984). *Anat. Rec.*, **208**, 589–594.

Hodgkinson CA, Moore KJ, Nakayama A, Steingrimsson E, Copeland NG, Jenkins NA and Arnheiter H. (1993). *Cell*, **74**, 395–404. PubMed

Hoeijmakers JH. (2001). *Nature*, **411**, 366–374. Article PubMed

Holbrook NJ and Fornace Jr AJ. (1991). *New Biol.*, **3**, 825–833. PubMed

Hollander MC, Kovalsky O, Salvador JM, Kim KE, Patterson AD, Haines DC and Fornace Jr AJ. (2001). *Cancer Res.*, **61**, 2487–2491. PubMed

Holman CD, Armstrong BK and Heenan PJ. (1983). *J. Natl. Cancer Inst.*, **71**, 651–656. PubMed

Howe HL, Wingo PA, Thun MJ, Ries LA, Rosenberg HM, Feigal EG and Edwards BK. (2001). *J. Natl. Cancer Inst.*, **93**, 824–842. Article PubMed

Hunt G, Kyne S, Wakamatsu K, Ito S and Thody AJ. (1995). *J. Invest. Dermatol.*, **104**, 83–85.

Husain Z, Pathak MA, Flotte T and Wick MM. (1991). *Cancer Res.*, **51**, 4964–4970.

Hwang BJ, Ford JM, Hanawalt PC and Chu G. (1999). *Proc. Natl. Acad. Sci. USA*, **96**, 424–428. Article PubMed

Insinga RP, Reither EN, Remington PL and Stephenson-Vine L. (2001). *WMJ*, **100**, 27–31.

Irwin C, Barnes A, Veres D and Kaidbey K. (1993). *Photochem. Photobiol.*, **57**, 504–507.

Islas AL and Hanawalt PC. (1995). *Cancer Res.*, **55**, 336–341. PubMed

Jeffers M, Rong S and Woude GF. (1996). *J. Mol. Med.*, **74**, 505–513. Article PubMed

Jemal A, Devesa SS, Hartge P and Tucker MA. (2001). *J. Natl. Cancer Inst.*, **93**, 678–683.

Jiang W, Ananthaswamy HN, Muller HK and Kripke ML. (1999). *Oncogene*, **18**, 4247–4253. Article PubMed

Jiang W, Ananthaswamy HN, Muller HK, Ouhtit A, Bolshakov S, Ullrich SE, El-Naggar AK and Kripke ML. (2001). *Proc. Natl. Acad. Sci. USA*, **98**, 9790–9795.

Jin S, Antinore MJ, Lung FD, Dong X, Zhao H, Fan F, Colchagie AB, Blanck P, Roller PP, Fornace Jr AJ and Zhan Q. (2000). *J. Biol. Chem.*, **275**, 16602–16608. PubMed

Jung EG. (1986). *Curr. Probl. Dermatol.*, **15**, 117–124.

Kaidbey KH and Kligman AM. (1979). *J. Invest. Dermatol.*, **72**, 253–256.

Kamada S, Shimono A, Shinto Y, Tsujimura T, Takahashi T, Noda T, Kitamura Y, Kondoh H and Tsujimoto Y. (1995). *Cancer Res.*, **55**, 354–359. PubMed

Karin M. (1995). *J. Biol. Chem.*, **270**, 16483–16486. PubMed

Kaskel P, Sander S, Kron M, Kind P, Peter RU and Krahn G. (2001). *Br. J. Dermatol.*, **145**, 602–609.

Kato M, Liu W, Akhand AA, Hossain K, Takeda K, Takahashi M and Nakashima I. (2000). *J. Invest. Dermatol.*, **115**, 1157–1158.

Kato M, Takahashi M, Akhand AA, Liu W, Dai Y, Shimizu S, Iwamoto T, Suzuki H and Nakashima I. (1998). *Oncogene*, **17**, 1885–1888. Article

Kawada A, Morimoto K, Hiruma M, Noda T and Ishibashi A. (1994). *J. Dermatol.*, **21**, 571–574.

Kazianis S, Gutbrod H, Nairn RS, McEntire BB, Della Coletta L, Walter RB, Borowsky RL, Woodhead AD, Setlow RB, Schartl M and Morizot DC. (1998). *Genes Chromosomes Cancer*, **22**, 210–220.

Kelsall SR and Mintz B. (1998). *Cancer Res.*, **58**, 4061–4065.

Kennedy C, ter Huurne J, Berkhout M, Gruis N, Bastiaens M, Bergman W, Willemze R and Bavinck JN. (2001). *J. Invest. Dermatol.*, **117**, 294–300.

Khlgatian MK, Hadshiew IM, Asawanonda P, Yaar M, Eller MS, Fujita M, Norris DA and Gilchrest BA. (2002). *J Invest. Dermatol.*, **118**, 126–132.

Klein-Parker HA, Warshawski L and Tron VA. (1994). *J. Cutan. Pathol.*, **21**, 297–301.

Knebel A, Rahmsdorf HJ, Ullrich A and Herrlich P. (1996). *EMBO J.*, **15**, 5314–5325. PubMed

Kraemer KH. (1994). *Jpn. J. Cancer Res.*, **85**, inside front cover.

Kulms D and Schwarz T. (2002). *J. Dermatol.*, **29**, 189–196.

Kusewitt DF and Ley RD. (1996). *Cancer Surv.*, **26**, 35–70.

Landi MT, Baccarelli A, Tarone RE, Pesatori A, Tucker MA, Hedayati M and Grossman L. (2002). *J. Natl. Cancer Inst.*, **94**, 94–101.

Langley RG and Sober AJ. (1997). *Cancer Invest.*, **15**, 561–567.

Larue L, Dougherty N and Mintz B. (1992). *Proc. Natl. Acad. Sci. USA*, **89**, 9534–9538.

Lerner AB, Shiohara T, Boissy RE, Jacobson KA, Lamoreux ML and Moellmann GE. (1986). *J. Invest. Dermatol.*, **87**, 299–304.

Ley RD. (1987). *Photodermatol.*, **4**, 173–175.

Ley RD. (2001). *Photochem. Photobiol.*, **73**, 20–23.

Ley RD. (2002). *Front. Biosci.*, **7**, d1531–d1534.

Ley RD, Applegate LA and Freeman SE. (1988). *Mutat. Res.*, **194**, 49–55.

Li G and Ho VC. (1998). *Br. J. Dermatol.*, **139**, 3–10. PubMed

Libow LF, Scheide S and DeLeo VA. (1988). *Pigment Cell Res.*, **1**, 397–401. PubMed

Linge C. (1996). *Cancer Surv.*, **26**, 71–87.

Liu SC, Parsons CS and Hanawalt PC. (1982). *J. Invest. Dermatol.*, **79**, 330–335. PubMed

MacKie RM. (1998). *Eur. J. Cancer*, **34**(Suppl 3), S3–S6.

Malitschek B, Fornzler D and Schartl M. (1995). *Bioessays*, **17**, 1017–1023.

Marks R. (2000). *Clin. Exp. Dermatol.*, **25**, 459–463.

Matsumura Y and Ananthaswamy HN. (2002). *Front. Biosci.*, **7**, d765–d783.

McGill GG, Horstmann M, Widlund HR, Du J,

Motyckova G, Nishimura EK, Liny, L, Ramaswamy S, Avery W, Ding HF, Jordan SA, Jackson IJ, Korsmeyer SJ, Golub TR and Fisher DE. (2002). *Cell*, **109**, 707–718. PubMed

McGovern VJ. (1952). *Med. J. Aust.*, 139–142.

McLane JA and Pawelek JM. (1988). *Biochemistry*, **27**, 3743–3747. PubMed

Medrano EE, Im S, Yang F and Abdel-Malek ZA. (1995). *Cancer Res.*, **55**, 4047–4052. PubMed

Mildner M, Eckhart L, Lengauer B and Tschachler E. (1999). *J. Invest. Dermatol.*, **113**, 1136–1137.

Mountjoy KG, Robbins LS, Mortrud MT and Cone RD. (1992). *Science*, **257**, 1248–1251. PubMed

Nairn RS, Kazianis S, McEntire BB, Della Coletta L, Walter RB and Morizot DC. (1996). *Proc. Natl. Acad. Sci. USA*, **93**, 13042–13047. Article PubMed

Nakayama K, Negishi I, Kuida K, Sawa H and Loh DY. (1994). *Proc. Natl. Acad. Sci. USA*, **91**, 3700–3704. PubMed

Nataraj AJ, Trent II JC and Ananthaswamy HN. (1995). *Photochem. Photobiol.*, **62**, 218–230. PubMed

Noonan FP, Otsuka T, Bang S, Anver MR and Merlino G. (2000). *Cancer Res.*, **60**, 3738–3743. PubMed

Noonan FP, Recio JA, Takayama H, Duray P, Anver MR, Rush WL, De Fabo EC and Merlino G. (2001). *Nature*, **413**, 271–272. Article PubMed

Norris W (1857). *Eight Cases of Melanosis with Pathological and Therapeutical Remarks on that Disease*. Longman: London.

Nylander K, Bourdon JC, Bray SE, Gibbs NK, Kay R, Hart I and Hall PA. (2000). *J. Pathol.*, **190**, 39–46. Article PubMed

Oltvai ZN, Milliman CL and Korsmeyer SJ. (1993). *Cell*, **74**, 609–619. PubMed

Ortonne JP. (2002). *Br. J. Dermatol.*, **146**(Suppl 61), 7–10.

Otsuka T, Takayama H, Sharp R, Celli G, LaRochelle WJ, Bottaro DP, Ellmore N, Vieira W, Owens JW, Anver M and Merlino G. (1998). *Cancer Res.*, **58**, 5157–5167. PubMed

Palmer JS, Duffy DL, Box NF, Aitken JF, O'Gorman LE, Green AC, Hayward NK, Martin NG and Sturm RA. (2000). *Am. J. Hum. Genet.*, **66**, 176–186.

Parker SL, Tong T, Bolden S and Wingo PA. (1997). *CA Cancer. J. Clin.*, **47**, 5–27. PubMed

Pavey S and Gabrielli B. (2002). *Cancer Res.*, **62**, 875–880.

Pavey S, Russell T and Gabrielli B. (2001). *Oncogene*, **20**, 6103–6110. Article PubMed

Plettenberg A, Ballaun C, Pammer J, Mildner M, Strunk D, Weninger W and Tschachler E. (1995). *Am. J. Pathol.*, **146**, 651–659.

Radler-Pohl A, Sachsenmaier C, Gebel S, Auer HP, Bruder JT, Rapp U, Angel P, Rahmsdorf HJ and Herrlich P. (1993). *EMBO J.*, **12**, 1005–1012. PubMed

Recio JA, Noonan FP, Takayama H, Anver MR, Duray P, Rush WL, Lindner G, De Fabo EC, DePinho RA and Merlino G. (2002). *Cancer Res.*, **62**, 6724–6730.

Reedy MV, Faraco CD and Erickson CA. (1998). *Dev. Dyn.*, **213**, 476–485.

Reinke V and Lozano G. (1997). *Radiat. Res.*, **148**, 115–122.

Rigel DS and Carucci JA. (2000). *CA Cancer. J. Clin.*, **50**, 215–236; quiz 237-40.

Romerdahl CA, Stephens LC, Bucana C and Kripke ML. (1989). *Cancer Commun.*, **1**, 209–216. PubMed

Rosenstein BS and Mitchell DL. (1987). *Photochem. Photobiol.*, **45**, 775–780. PubMed

Rosette C and Karin M. (1996). *Science*, **274**, 1194–1197. Article PubMed

Runger TM, Epe B and Moller K. (1995). *J. Invest. Dermatol.*, **104**, 68–73.

Sachsenmaier C, Radler-Pohl A, Zinck R, Nordheim A, Herrlich P and Rahmsdorf HJ. (1994). *Cell*, **78**, 963–972. PubMed

Schaffer JV and Bolognia JL. (2001). *Arch. Dermatol.*, **137**, 1477–1485.

Scharffetter-Kochanek K, Wlaschek M, Brenneisen P, Schauen M, Blaudschun R and Wenk J. (1997). *Biol. Chem.*, **378**, 1247–1257.

Schartl A, Malitschek B, Kazianis S, Borowsky R and Schartl M. (1995). *Cancer Res.*, **55**, 159–165.

Scott G, Stoler M, Sarkar S and Halaban R. (1991).

J. Invest. Dermatol., **96**, 318–322. PubMed

Scott MC, Wakamatsu K, Ito S, Kadekaro AL, Kobayashi N, Groden J, Kavanagh R, Takakuwa T, Virador V, Hearing VJ and Abdel-Malek ZA. (2002). *J. Cell Sci.*, **115**, 2349–2355.

Setlow RB, Grist E, Thompson K and Woodhead AD. (1993). *Proc. Natl. Acad. Sci. USA*, **90**, 6666–6670. PubMed

Setlow RB and Woodhead AD. (1994). *Mutat. Res.*, **307**, 365–374.

Setlow RB, Woodhead AD and Grist E. (1989). *Proc. Natl. Acad. Sci. USA*, **86**, 8922–8926. PubMed

Shaulian E, Schreiber M, Piu F, Beeche M, Wagner EF and Karin M. (2000). *Cell*, **103**, 897–907. PubMed

Shih IM and Herlyn M. (1994). *In Vivo*, **8**, 113–123. PubMed

Smith ML, Ford JM, Hollander MC, Bortnick RA, Amundson SA, Seo YR, Deng CX, Hanawalt PC and , Fornace Jr AJ. (2000). *Mol. Cell Biol.*, **20**, 3705–3714. Article PubMed

Smith R, Healy E, Siddiqui S, Flanagan N, Steijlen PM, Rosdahl I, Jacques JP, Rogers S, Turner R, Jackson IJ, Birch-Machin MA and Rees JL. (1998). *J. Invest. Dermatol.*, **111**, 119–122.

Smith ML and Seo YR. (2002). *Mutagenesis*, **17**, 149–156. Article PubMed

Suzuki I, Im S, Tada A, Scott C, Akcali C, Davis MB, Barsh G, Hearing V and Abdel-Malek Z. (1999). *J. Invest. Dermatol. Symp. Proc.*, **4**, 29–34.

Tada A, Suzuki I, Im S, Davis MB, Cornelius J, Babcock G, Nordlund JJ and Abdel-Malek ZA. (1998). *Cell Growth Differ.*, **9**, 575–584. PubMed

Takahashi S, Saito S, Ohtani N and Sakai T. (2001). *Cancer Res.*, **61**, 1187–1195. PubMed

Takayama H, LaRochelle WJ, Sharp R, Otsuka T, Kriebel P, Anver M, Aaronson SA and Merlino G. (1997). *Proc. Natl. Acad. Sci. USA*, **94**, 701–706. Article PubMed

Takimoto R, MacLachlan TK, Dicker DT, Niitsu Y, Mori T and el-Deiry WS. (2002). *Cancer Biol. Ther.*, **1**, 177–186.

Taylor SC. (2002). *J. Am. Acad. Dermatol.*, **46**, S41–S62.

Thody AJ. (1999). *Ann. NY Acad. Sci.*, **885**, 217–229.

Thody AJ and Graham A. (1998). *Pigment Cell Res.*, **11**, 265–274. PubMed

Tibbetts RS, Brumbaugh KM, Williams JM, Sarkaria JN, Cliby WA, Shieh SY, Taya Y, Prives C and Abraham RT. (1999). *Genes Dev.*, **13**, 152–157. PubMed

Tornaletti S and Pfeifer GP. (1994). *Science*, **263**, 1436–1438. PubMed

Tornaletti S and Pfeifer GP. (1996). *Bioessays*, **18**, 221–228. PubMed

Tucker MA, Greene MH, Clark Jr WH, Kraemer KH, Fraser MC and Elder DE. (1983). *J. Pediatr.*, **103**, 65–69.

Unsal-Kacmaz K, Makhov AM, Griffith JD and Sancar A. (2002). *Proc. Natl. Acad. Sci. USA*, **99**, 6673–6678. Article PubMed

Valverde P, Healy E, Sikkink S, Haldane F, Thody AJ, Carothers A, Jackson IJ and Rees JL. (1996). *Hum. Mol. Genet.*, **5**, 1663–1666. PubMed

van den Oord JJ, Vandeghinste N, De Ley M and De Wolf-Peeters C. (1994). *Am. J. Pathol.*, **145**, 294–300. PubMed

Van Dyke T and Jacks T. (2002). *Cell*, **108**, 135–144. PubMed

Wan YS, Wang ZQ, Shao Y, Voorhees JJ and Fisher GJ. (2001). *Int. J. Oncol.*, **18**, 461–466. PubMed

Wang SQ, Kopf AW, Marx J, Bogdan A, Polsky D and Bart RS. (2001a). *J. Am. Acad. Dermatol.*, **44**, 767–774.

Wang SQ, Setlow R, Berwick M, Polsky D, Marghoob AA, Kopf AW and Bart RS. (2001b). *J. Am. Acad. Dermatol.*, **44**, 837–846. PubMed

Wang XW, Yeh H, Schaeffer L, Roy R, Moncollin V, Egly JM, Wang Z, Freidberg EC, Evans MK, Taffe BG *et al*. (1995). *Nat. Genet.*, **10**, 188–195. PubMed

Wang Y and Becker D. (1997). *Nat. Med.*, **3**, 887–893. PubMed

Whiteman DC, Whiteman CA and Green AC. (2001). *Cancer Causes Control*, **12**, 69–82.

Wiltshire RN, Duray P, Bittner ML, Visakorpi T, Meltzer PS, Tuthill RJ, Liotta LA and Trent JM. (1995). *Cancer Res.*, **55**, 3954–3957. PubMed

Wittbrodt J, Adam D, Malitschek B, Maueler W, Raulf F, Telling A, Robertson SM and Schartl M. (1989). *Nature*, **341**, 415–421. PubMed

Wittbrodt J, Lammers R, Malitschek B, Ullrich A and Schartl M. (1992). *EMBO J*, **11**, 4239–4246. PubMed

Wong G, Pawelek J, Sansone M and Morowitz J. (1974). *Nature*, **248**, 351–354.

Wright JA, Keegan KS, Herendeen DR, Bentley NJ, Carr AM, Hoekstra MF and Concannon P. (1998). *Proc. Natl. Acad. Sci. USA*, **95**, 7445–7450. Article PubMed

Xiao GH, Jeffers M, Bellacosa A, Mitsuuchi Y, Vande Woude GF and Testa JR. (2001). *Proc. Natl. Acad. Sci. USA*, **98**, 247–252. PubMed

Yaar M and Gilchrest BA. (2001). *Clin. Exp. Dermatol.*, **26**, 583–591.

Yamamura K, Kamada S, Ito S, Nakagawa K, Ichihashi M and Tsujimoto Y. (1996). *Cancer Res.*, **56**, 3546–3550.

Yang Q, Manicone A, Coursen JD, Linke SP, Nagashima M, Forgues M and Wang XW. (2000). *J Biol. Chem.*, **275**, 36892–36898. PubMed

You YH, Lee DH, Yoon JH, Nakajima S, Yasui A and Pfeifer GP. (2001). *J Biol. Chem.*, **276**, 44688–44694. PubMed

Ziegler A, Jonason AS, Leffell DJ, Simon JA, Sharma HW, Kimmelman J, Remington L, Jacks T and Brash DE. (1994). *Nature*, **372**, 773–776. PubMed

Figures

Figure 1 Molecular and carcinogenic responses of melanocytes to UV radiation. Shown is a highly simplified schematic summary of proposed immediate and delayed responses of melanocytes to UV. Some pathways are inferred from reported data generated from keratinocytes or fibroblasts. More speculative UV-associated pathways are dashed. Most cellular responses to UV radiation are the direct result of incurred DNA damage, typically 6–4 photoproducts (6–4PP) and pyrimidine dimers (PD) generated from UVB (red ovals), and oxidative damage from UVA. DNA damage responses are mediated by p53, which can trigger transcription of numerous downstream genetic targets (green boxes). DNA repair genes are activated, including Gadd45a and several members of the XP gene family, stimulating NER or BER pathways. Proliferating melanocytes with damaged DNA can be growth arrested in G1 or G2 prior to repair. In most cases, DNA damage is readily repaired, restoring melanocytes to normalcy. In

nonmelanocytic skin cells, irreparable DNA damage triggers p53-dependent apoptosis through Bax. However, because melanocytes produce abundant levels of the prosurvival factor Bcl2, they may survive with excessive DNA damage, perpetuated as mutations in future generations (purple boxes). Melanocyte progenitors, a growing subpopulation more prevalent in younger skin, may be more susceptible to this outcome. It is likely that the resulting mutant melanocytes constitute the cellular pool from which melanoma eventually arises. UV also affects cell cycle arrest and apoptosis through pathways independent of DNA damage. Pigmentation represents a melanocyte-specific response to UV irradiation mediated through MC1R, normally stimulated by αMSH. Major differentiation genes, such as those encoding tyrosinase and TRP1, are targets of p53 as well. UV can also directly activate cell surface growth factor receptors, including RTKs, thereby inducing a variety of critical pathways, including antiapoptotic signaling through Akt, and growth stimulation through MAPK. Notably, BRAF, mutated in the majority of human melanomas, may represent a key relay point for signals regulating both melanocyte growth and differentiation. See the text for detail

Figure 2 UV-inducible melanomagenesis in the HGF/SF transgenic mouse. Dermal melanomas arise in untreated HGF/SF transgenic mice with a mean onset age of approximately 21 months, a latency that was not overtly altered in response to chronic adult suberythemal, or nonskin reddening, UV irradiation (UV doses from an FS40 sunlamp graded from 2.3 to 6.0 kJ/m^2 three times weekly) (Noonan *et al.*, 2000). In contrast, a single erythemal dose (9.6 kJ/m^2) from the same sunlamp to 3.5-day-old neonatal HGF/SF transgenic mice induced cutaneous melanoma with significantly reduced latency (Noonan *et al.*, 2001). Moreover, the UV-induced murine melanomas frequently resembled their human counterpart with respect to histopathological appearance and graded progression. Exposure of HGF/SF transgenic neonates to a second erythemal dose of UV irradiation did not accelerate melanomagenesis; however, the dual exposure did significantly increase the number of melanocytic lesions arising per mouse (Noonan *et al.*, 2001)

---

19 May 2003, Volume 22, Number 20, Pages 3099-3112

Table of contents Previous Article Next PDF